obvious over Brosch or Mahairas in view of Altschul *et al., J. Mol. Bio.* 215: 403-410 (1990) ("Altschul"). Claims 1-23 are rejected under 35 U.S.C. §103(a) on the basis that they are obvious over Brosch or Mahairas. Applicants respectfully traverse these objections and rejections.

37 C.F.R. §1.75 (c):

Claims 7-9 were objected to under 37 C.F.R. §1.75 (c) as allegedly improper dependent claims. The Examiner states that each claim fails to further limit the subject matter of the base claim. While Applicants respectfully disagree with the Examiner's position, Applicants cancel claims 7-9 herein and request that the objection be withdrawn.

35 U.S.C. §112, second paragraph, indefiniteness:

Claims 1-23 were rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. The Examiner states that the phrases "relationship between the members", "difference in observed relationship", and "expected relationship" in claim 1 are vague and unclear. Applicants respectfully disagree.

The specification defines the term "relationship" on page 8, lines 24-28. The specification states that the term refers to terminal sequences or their corresponding sequences and refers to the relative position of the sequences in the genome. For example, the term refers to the physical distance between two sequences, whether the sequences are present on the same vector or whether the sequences are on the same chromosome.

The specification provides additional examples of the meanings of the terms at least on page 24, line 5 - page 25, line 10. The specification states that the terminal sequences are obtained, the relationship between the sequences is determined and the relationship is compared to the relationship of the corresponding sequences in the reference genome. A comparison of the relationship of the sequences from the test genome and the corresponding sequences in the reference genome reveals if the sets of

sequences are collinear, or if there has been an insertion, a deletion, an inversion, or a translocation event in the DNA between the ends sequenced.

In view of the disclosure in the specification, Applicants submit that one of skill in the art would be reasonable appraised of the scope of the invention. In view of the above remarks Applicants respectfully request that the §112, second paragraph rejection of claims 1-23 be withdrawn.

35 U.S.C. §102(b):

Claims 1, 3, and 11 were rejected under 35 U.S.C. §102(b) on the basis that they are anticipated by Brosch or Mahairas. The Examiner states that Brosch anticipates the claimed invention by teaching a plurality of *M. tuberculosis* BAC clones with determined terminal sequences and that these clones can be used for comparative genomics. The Examiner states that Mahairas teaches BAC cloned sequence tags that are end sequenced and which can be used to compare with a reference genome. Applicants respectfully disagree that either Brosch or Mahairas anticipate claims 1, 3, and 11.

The Examiner is reminded that a reference may anticipate a claim under 35 U.S.C. §102(b) only if it contains each and every element of the claimed invention and it was published more than one year before the application date of the claim. As explained below, Brosch and Mahairas do not contain each and every element of the claimed invention either alone or in combination.

As recited in claim 1, the present invention relates to methods of rapidly identifying genomic rearrangements in a test genome relative to a reference genome. The method comprises the steps of cloning fragments of a test genome in to a suitable vector, sequencing the insert termini, identifying the corresponding sequences in a reference genome and identifying differences in the relationship of the sequences in the test genome relative to the reference genome. Applicants amend claim 1 herein to clarify that the test genome is obtained from an individual with a disease *e.g.* cancer. The **invention is directed to rapidly identifying differences between a test (disease) genome and a**

reference genome in order to improve disease diagnosis and prognosis, and identify targets for therapeutic intervention (see specification, page 1, lines 5-7 and 22-28).

Claim 1 recites:

> A method for **comparing a test genome to a reference genome**, said method comprising:
> (i) providing a plurality of clones of known size that substantially cover at least a portion of said test genome;
> (ii) obtaining sequence information from the termini of each of said plurality of clones, thereby **obtaining a pair of terminal sequences**;
> (iii) **identifying a pair of sequences within said reference genome that corresponds to each of said pairs of terminal sequences**; and
> (iv) determining the relationship between the members of each pair of corresponding sequences within said reference genome;
> wherein a difference in the observed relationship between the members of any of said pairs of corresponding sequences within said reference genome and the expected relationship based upon said known size of said plurality of clones indicates the presence of a rearrangement in said test genome compared to said reference genome and **wherein said test genome is obtained from an individual with a disease** (emphasis added).

The Examiner has failed to identify each and every element of the claimed invention in the references. Brosch discloses a plurality of *M. tuberculosis* BAC clones which were end sequenced. The BAC clones were used as part of, and to complete the sequencing of, the same genome, which is a reference genome (see page 2228 column 1, first paragraph). However, Brosch fails to teach constructing a BAC library of a genome from an individual with a disease, sequencing the ends of the genome inserts in the BAC clones and comparing the genome BAC clone sequences to a second (reference) genome. The Examiner has failed to point out where Brosch teaches these elements of the claimed invention.

Brosch teaches comparing an *M. bovis* test genome to the *M. tuberculosis* reference BAC clones by Southern blot hybridizations (see Brosch, page 2226 column 1 and Figure 4). *M. tuberculosis* sequences which did not hybridize to *M. bovis* sequences

were analyzed further. Brosch does not teach making *M. bovis* genomic fragments, inserting those fragments into a vector, sequencing the insert termini, identifying the corresponding sequences in the *M. tuberculosis* genome and comparing the relationship of the *M. bovis* sequences to the relationship of the corresponding *M. tuberculosis* sequences, which are the elements of claim 1. Brosch also fails to teach that the *M. bovis* genome is from an organism with a disease. For the reasons discussed above, Brosch fails to teach all of the elements of the claimed invention and, therefore, Brosch fails as a §102(b) reference. Applicants respectfully request that the §102(b) rejection based on Brosch be withdrawn.

Mahairas also fails to teach all of the elements of the claims. Mahairas teaches generating a plurality of BAC clones containing randomly cleaved human genome inserts, sequencing the ends of the inserts and generating a restriction map fingerprint of each clone. This information is then used to order the BAC clones as overlapping BAC clones are sequenced (see abstract, page 9739). Ultimately, this information will be used to put together a complete reference human genome sequence.

Similar to Brosch, Mahairas fails to teach making BAC clones containing test genome inserts, sequencing the ends of the test genome inserts and comparing the sequence information to the corresponding sequences in a reference genome to identify differences or changes in the relationship of the sequences in the test genome relative to the reference genome as claimed. Mahairas also fails to teach that the test genome is from an individual with a disease. The Examiner points to the abstract and page 9743, second paragraph of Mahairas for teaching these elements of the claims.

As discussed above, a review of the abstract and the second paragraph of page 9743 indicates that the sequence information and restriction enzyme maps of the BAC clones containing human genomic inserts are used to order the BAC clones relative to other data provided and ultimately to construct the sequence of the ***same*** human genome from which they were derived, not a ***different*** reference genome. These sections do not teach making a BAC library containing test human genome inserts using DNA isolated from an individual with a disease, sequencing the insert ends and comparing

them to a reference human genome as claimed. In view of the above remarks and in view of the failing of Mahairas to teach all of the elements of the claims, Applicants respectfully request that the §102(b) rejection of claims 1, 3 and 11 based on Mahairas be withdrawn.

35 U.S.C. §103(a):

Claim 1 is rejected under 35 U.S.C. §103(a) as allegedly obvious over Brosch or Mahairas in view of Altschul. Claims 1-23 are rejected under 35 U.S.C. §103(a) on the basis that they are obvious over Brosch or Mahairas. The Examiner states that claim 1 is rejected as obvious over Brosch or Mahairas in view of Altschul because the primary references teach end sequence profiling of a library of clones and of the numerous computational methods used for nucleic acid comparisons, Altschul's BLAST method is the best known. The Examiner states that claims 1-23 are rejected because if there are any differences between Brosch and Mahairas and the claimed invention they are minor in nature. Applicants respectfully disagree.

The Examiner is respectfully reminded that in order to find an invention *prima facie* obvious, the cited art must (1) teach each and every element of the claimed invention, (2) provide suggestion or motivation to combine or modify the references, and (3) provide a reasonable expectation that one could successfully arrive at the claimed invention. See M.P.E.P. §2143 *et seq.* The Examiner has failed to make his *prima facie* case because the cited art does not teach each and every element of the claimed invention and does not provide a reasonable expectation of successfully arriving at the claimed invention.

Brosch or Mahairas in combination with Altschul do not teach each and every element of the claimed invention. As discussed above, the Examiner has failed to show where Brosch or Mahairas teaches constructing a BAC library of a test (disease) genome, sequencing the ends of the test genome BAC clones and comparing the test genome BAC clone sequences to a reference genome to identify changes in the

relationship of the sequences in the test genome relative to the reference genome as claimed.

Brosch and Mahairas do teach making genomic libraries in BAC clones and end sequencing the genomic inserts. However, as discussed above, Brosch and Mahairas are directed to creating the reference genome. They are not directed to analyzing a test genome against a reference genome.

The deficiencies of Brosch and Mahairas are not remedied by Altschul. Altschul discloses a method of searching a database with a query nucleotide or peptide sequence and identifying homologs (*e.g.* corresponding sequences, if any) of that sequence. Altschul does not teach or suggest determining the relationship of test sequences to one another, identifying the relationship of the corresponding sequences in a reference genome and identifying differences between the relationship of the test sequences and the corresponding sequences. As such, the Examiner has failed to make his *prima facie* case of obviousness by failing to cite references which teach each and every element of the claimed invention. Because the cited references do not teach every element of the claimed invention, one of skill would not have a reasonable expectation of arriving at the claimed invention by combining the references. In view of the above remarks, Applicants respectfully request that the §103(a) rejection of claim 1 based on Brosch or Mahairas, in view of Altschul, and the §103(a) rejection of claims 1-23 based on Brosch or Mahairas be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A method for comparing a test genome to a reference genome, said method comprising:

(i) providing a plurality of clones of known size that substantially cover at least a portion of said test genome;

(ii) obtaining sequence information from the termini of each of said plurality of clones, thereby obtaining a pair of terminal sequences;

(iii) identifying a pair of sequences within said reference genome that corresponds to each of said pairs of terminal sequences; and

(iv) determining the relationship between the members of each pair of corresponding sequences within said reference genome;

wherein a difference in the observed relationship between the members of any of said pairs of corresponding sequences within said reference genome and the expected relationship based upon said known size of said plurality of clones indicates the presence of a rearrangement in said test genome compared to said reference genome and wherein said test genome is obtained from an individual with a disease.